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ORIGINAL RESEARCH ARTICLE

Survey of Physicians' Understanding of Specific Risks Associated with Retigabine

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Abstract

Background Following reports of discoloration, including retinal pigmentation, in addition to known significant risks of urinary retention, central nervous system effects, and QTc prolongation, the retigabine indication was restricted to adjunctive treatment of partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.

Objective To ascertain the effectiveness of educational initiatives as reflected in physicians' understanding of retigabine-associated risks, management, and patient selection.

Methodology An online, cross-sectional survey, designated a post-authorization safety study (24/9/2014–30/1/2015), recruited retigabine prescribers (RP) and retigabine non-prescribers (RNP) in seven countries, who had been sent a retigabine Dear Health Care Professional letter (June 2013). Questions tested understanding of the significant risks associated with retigabine.

Results 414/467 participants completed all questions (RP, $n = 141$; RNP, $n = 273$) and were included in the analysis. 74.2 % of these participants (RP, 77.3 %; RNP, 72.5 %) correctly identified the label indication. 81.9 % of participants (RP, 86.5 %; RNP, 79.5 %) recognized that specific retigabine-associated risks included pigment changes of ocular tissues, including the retina. 81.6 % of participants (RP, 87.2 %; RNP, 78.8 %) recognized that a comprehensive ophthalmologic examination is required. 99.8 % of participants (RP, 100.0 %; RNP, 99.6 %) acknowledged the requirement for action in case of retinal pigmentation or vision changes. RP and RNP results were similar to the overall participants' analysis, with a trend toward stronger understanding among RP.

Conclusion Most participants recognized the appropriate population for retigabine treatment and the requirement to monitor for adverse events including retinal pigmentation and vision changes. Understanding was satisfactory among RNP but stronger among RP.

Key Points

A seven-country survey, following a Dear Health Care Professional (DHCP) letter, assessed physicians' knowledge of the significant risks associated with retigabine therapy and revisions to the product information.

Most physicians participating in the survey were aware of the requirement to monitor for treatment-emergent adverse events including retinal pigmentation and vision changes, and could identify the appropriate population for retigabine treatment.

Understanding was stronger among retigabine prescribers than non-prescribers, for physicians who specialized in epilepsy, and for physicians treating higher rather than lower numbers of epilepsy patients per month.

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1 Introduction

Retigabine (Trobalt™; GlaxoSmithKline [GSK]) was approved in Europe in March 2011 as adjunctive therapy for the management of drug-resistant partial-onset seizures with or without secondary generalization in adults 18 years and older with epilepsy [1]. The results of randomized studies comparing retigabine and placebo for efficacy and safety indicated that although effective, retigabine treatment entailed increased risks of urinary retention, central nervous system effects (including confusion, hallucinations, and psychotic disorders), and prolongation of the QTc interval [2–5]. Subsequently, adverse event reports, and coincidental findings at study visits, of pigmentation/discoloration were received from long-term, open-label extension studies and a compassionate use program. Reports were generally of a blue-grey discoloration of the nails and/or lips; pigmentation of the skin and retina was also reported [6]. An increase in such reports over time prompted a decision by GSK Global Clinical Safety and Pharmacovigilance in 2013 to restrict the retigabine indication to adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years and older, *where other appropriate drug combinations have proved inadequate or have not been tolerated* [7]. In addition, warnings of pigment changes (discoloration) of ocular tissues including the retina, as well as of the lips, skin, and nails were added to the Summary of Product Characteristics (SmPC; sections 4.4 and 4.8) [8], with recommendations for ophthalmologic examinations before and during treatment. At the same time, in the USA, where the drug was marketed as ezogabine (Potiga®), the Food and Drug Administration (FDA) approved changes to the label describing risks of abnormalities in the retina, potential vision loss, and skin discoloration [9, 10]. Attention was drawn to these risks in a Drug Safety Communication in April 2013 [11].

After educational outreach to neurologists in the first seven European countries to launch retigabine (Denmark, Germany, Norway, Slovakia, Spain, Switzerland, and the UK), focusing on the risks described in the approved European Union Physician's Guide for retigabine, results of a follow-up online survey (November 2012–October 2013) indicated that physicians generally had adequate knowledge of the indication for retigabine, but had poorer recall of specific dose-related information and risk management [12].

Subsequent to the 2012–2013 survey [12], GSK made further changes to the product labeling for retigabine, and, in June 2013, sent a Dear Health Care Professional (DHCP) letter to inform physicians in Europe and Hong Kong of the revisions to the indication and wording in the SmPC, and recommending that ophthalmologic examinations be performed at baseline and at least every 6 months thereafter during treatment with retigabine. The letter also reminded physicians of the need to assess benefits versus risks when initiating or continuing retigabine therapy. Following this initiative, which was specified in the Risk Management Plan (RMP), the present post-authorization safety study (PASS) survey was directed to physicians across seven countries to ascertain the effectiveness of the DHCP letter and to evaluate physicians' awareness and knowledge of the specific risks associated with retigabine (including retinal pigmentation, skin discoloration, urinary retention, prolongation of the QTc interval, and psychiatric disorders), management of such risks, new safety-monitoring activities, and the appropriate patient population for treatment.

2 Methods

2.1 Study Design

The PASS was designed as an online cross-sectional survey (24 September 2014–30 January 2015) of a sample of physicians, divided equally between retigabine prescribers (RP) and retigabine non-prescribers (RNP), who met the following criteria: (1) they had prescribed an antiepileptic drug (AED) at least once in the previous 6 months; (2) they had been sent a retigabine DHCP letter in June 2013; and (3) they practiced medicine in one of four countries within the European Union (EU) where retigabine had been used comparatively often (Belgium, Spain, Slovakia, and the UK) or three countries outside the EU where retigabine is available (Switzerland, Norway, and Hong Kong, China). Physicians were ineligible to participate if they were employees of GSK or United BioSource Corporation, or were government officials. Ethics approval was obtained as required by individual countries, as was regulatory approval or notification where applicable. Physicians to whom the DHCP letter had been sent were invited to participate in the survey by e-mail in Spain and by postal mail in the other countries, where e-mail addresses were not available.

The online survey questionnaire consisted of 16 questions, of which nos. 1–9 were the screening phase and nos. 10–15 were the assessment phase; no. 16 was a purely administrative question by the independent third party engaged to conduct the survey. The screening questions (1–9) were designed to eliminate ineligible respondents (as above) and to classify the eligible participants as either RP or RNP. Eligible participants were asked to state the time elapsed since they last wrote a prescription for any AED and whether they had ever prescribed retigabine. To

identify current RP, eligible participants were further asked to state whether they currently had patients who were taking retigabine and the last time they had initiated a patient on retigabine.

Survey assessment questions (nos. 10–15) were designed to test understanding of the significant risks associated with retigabine. Questions were multiple choice and closed ended. Survey questionnaires were programmed to ensure that questions were asked in a logical sequence. Certain questions required a specific answer in order for the participant to proceed to the next question. Participants could not go back to a question once the question had been answered, and could not skip ahead if they did not meet the criteria to skip questions. Except for data omitted in the skip pattern, no missing data were expected. All questions had to be answered in numerical order to complete the survey; only completed surveys were analyzed. Responses to questions related to knowledge, attitudes, and behaviors were categorized as "correct" or "incorrect"; "I don't know" was categorized as an incorrect response.

2.2 Statistical Methods

The statistical analysis was descriptive; no formal hypotheses were tested. Counts and percentages were calculated for each item in the questionnaire. Unless otherwise indicated, percentages were based on the population to whom a specific question was presented. Confidence intervals (CIs) were exact two-sided 95 % CIs; no adjustment was performed for multiplicity. Planned subgroup analyses of the responses to all questions related to understanding of the risks associated with retigabine were stratified by respondents' primary specialties and by the number of patients with epilepsy treated per month. All analyses were produced using SAS Software Version 9.1 (Cary, NC, USA).

3 Results

Invitations were sent to 7335 physicians and were followed up with reminder letters ($N = 13{,}085$). The first follow-up was sent to all non-respondents, whether RP or RNP, requesting them to complete the survey. When the sample size for RNP was reached, the survey was closed earlier (28 October 2014) for that group and extended for RP (30 January 2015). In an effort to meet the sample RP target after the closure of RNP recruitment, a second follow-up letter was sent to non-respondents asking only current RP to complete the survey. At the close of recruitment, of 467 respondents who were screened for participation, 426 (91.2 %) were considered eligible. Although RP did not reach the target of 200, the numbers in each group were considered sufficient for analysis. Of the 467 physicians who accessed the survey, 414 (88.7 %) (Table 1) completed the questionnaire and were included in the analysis (RP, $n = 141$; RNP, $n = 273$).

Table 1 Survey administration results: recruitment

Invitation process	Responses *N* (%)[a]
Invitation letters sent	7335
Reminders sent	13,085
Respondents screened for participation[b]	467 (100.0)
Respondents eligible to participate[c]	426 (91.2)
Eligible respondents who completed the survey (participants[d])	414 (88.7)

[a] Percentages based on number of screened respondents

[b] Screened respondents included all physicians who accessed the online survey using the unique code provided, and answered the first question with any response

[c] Respondents were ineligible to participate if they were employees of GSK or UBC, or government officials

[d] Participants were those who answered all inclusion/exclusion questions

Demographic information, including country of residence, type of practice, and number of patients with epilepsy being treated, was collected to further characterize the participant population included in the analysis (Table 2). Approximately half (52.7 %) of participants reported their primary medical specialty as General Neurology; 38.2 % reported a specialty in Neurology with an Interest in Epilepsy Treatment; 8.5 % self-identified as Epilepsy specialists/Epileptologists. Approximately half of the participants were treating 11–50 epilepsy patients ($n = 218$, 52.7 %) and about a quarter were treating 1–10 epilepsy patients ($n = 100$, 24.2 %) per month (data not shown). The remaining participants treated between 51 and 100 patients ($n = 73$, 17.6 %) or $\geq$101 patients ($n = 23$, 5.6 %) with epilepsy per month. The highest proportion of participants came from Spain (44.9 %), followed by Slovakia (15.9 %), the UK (15.2 %), and Belgium (12.3 %) (Table 2). Almost half (48.9 %) of RP reported having initiated a patient on retigabine therapy within the previous 6 months; more than a quarter (28.3 %) had done so within the previous 1–3 months (Table 2).

3.1 Survey Responses

Responses to all questions related to understanding of the specific risks associated with retigabine are shown in Table 3. About three-quarters of overall participants (74.2 %; RP, 77.3 %; RNP, 72.5 %) correctly identified that the current label indication for retigabine is "approved for use in adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations

Table 2 Demographic characteristics of participating physicians

Question	Current RP $N = 141$		Current RNP $N = 273$		All participants $N = 414$	
	n	%	*n*	%	*n*	%
Question 3: How would you classify your primary medical specialty?						
Epilepsy or epileptology	27	19.1	8	2.9	35	8.5
Neurology with an interest in the treatment of epilepsy	56	39.7	102	37.4	158	38.2
General Neurology	57	40.4	161	59.0	218	52.7
Neuropsychiatry	0	0.0	2	0.7	2	0.5
Neurosurgery	1	0.7	0	0.0	1	0.2
Question 4: In what country is your primary medical practice?						
Spain	56	39.7	130	47.6	186	44.9
Slovakia	28	19.9	38	13.9	66	15.9
UK	13	9.2	50	18.3	63	15.2
Belgium	23	16.3	28	10.3	51	12.3
Switzerland	12	8.5	17	6.2	29	7.0
Norway	7	5.0	10	3.7	17	4.1
Hong Kong	2	1.4	0	0.0	2	0.5
Question 9: When was the last time you initiated a patient on TROBALT (retigabine)?						
In the last month	13	9.2	0	0.0	13	3.1
In the last 3 months	27	19.1	5	1.8	32	7.7
Between 3 and 6 months	29	20.6	6	2.2	35	8.5
Between 6 and 12 months	39	27.7	32	11.7	71	17.1
More than 12 months ago	33	23.4	61	22.3	94	22.7
Question not asked (Answered *No* or *I don't know* to Question 7: Have you ever prescribed TROBALT (retigabine)? (used to ensure that the sample includes the minimal number of Trobalt prescribers)			169	61.9	169	40.8
a. Yes						
b. No [Go to Q10]						

Values may not add up to 100 % due to rounding

RNP retigabine non-prescribers, *RP* retigabine prescribers

have proved inadequate or have not been tolerated." Overall, 81.9 % (RP, 86.5 %; RNP, 79.5 %) recognized that the specific risks associated with retigabine included pigment changes (discoloration) of ocular tissues, including the retina. Additionally, 81.6 % overall (RP, 87.2 %; RNP, 78.8 %) identified that according to the safety monitoring measures in the current product label, a comprehensive ophthalmologic examination is required at baseline and at least every 6 months thereafter while treatment is ongoing. Similar percentages among the RP and RNP groups identified the following specific risks associated with retigabine: pigment changes (discoloration) of nails, lips, and/or skin (overall, 71.5 %; RP, 77.3 %; RNP, 68.5 %); urinary retention (overall, 67.4 %; RP, 75.9 %; RNP, 63.0 %); psychotic disorders including confusional state and hallucinations (overall, 72.2 %; RP, 78.7 %; RNP, 68.9 %); and QTc prolongation (overall, 65.7 %; RP, 75.2 %; RNP, 60.8 %). Results analyzed by RP and RNP were similar to the overall analysis, but a trend indicated a better level of understanding of retigabine-associated risks among RP. Participants overall were generally familiar with retigabine's risk profile, particularly the risk of pigmentary changes (Table 3).

Overall, 99.8 % of participants (RP, 100.0 %; RNP, 99.6 %) correctly acknowledged that action was required if retinal pigmentation or vision changes were detected in a patient taking retigabine. Approximately half of participants (53.1 %; RP, 51.8 %; RNP, 53.8 %) identified that physicians should carefully reassess benefits versus risks before deciding whether to continue or cease retigabine administration. Slightly less than half of participants (48.6 %; RP, 51.1 %; RNP, 47.3 %) selected that retigabine should be discontinued if another suitable AED was available.

Results summarized by primary specialty for physicians who completed the survey are shown in Table 4. Analysis of responses by the primary specialties of Epilepsy/

Table 3 Responses to all questions related to understanding of the risks associated with retigabine

Question	RP $N = 141$		RNP $N = 273$		All participants $N = 414$	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Question 10: According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:						
Monotherapy of partial onset seizures	1	0.7	1	0.4	2	0.5
Adjunctive treatment of partial onset seizures	30	21.3	60	22.0	90	21.7
Adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated[a]	**109**	**77.3 (69.5–83.9)**	**198**	**72.5 (66.8–77.7)**	**307**	**74.2 (69.7–78.3)**
Status epilepticus	0	0.0	0	0.0	0	0.0
I don't know	1	0.7	14	5.1	15	3.6
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes," "no," or "I don't know" for each of the following:						
Pigment changes (discoloration) of ocular tissues, including the retina						
Yes[a]	**122**	**86.5 (79.8–91.7)**	**217**	**79.5 (74.2–84.1)**	**339**	**81.9 (77.8–85.5)**
No	7	5.0	20	7.3	27	6.5
I don't know	12	8.5	36	13.2	48	11.6
Pigment changes (discoloration) of the nails, lips, and/or skin						
Yes[a]	**109**	**77.3 (69.5–83.9)**	**187**	**68.5 (62.6–74.0)**	**296**	**71.5 (66.9–75.8)**
No	14	9.9	33	12.1	47	11.4
I don't know	18	12.8	53	19.4	71	17.1
Respiratory distress						
Yes	9	6.4	12	4.4	21	5.1
No[a]	**90**	**63.8**	**155**	**56.8**	**245**	**59.2**
I don't know	42	29.8	106	38.8	148	35.7
Urinary retention						
Yes[a]	**107**	**75.9 (68.0–82.7)**	**172**	**63.0 (57.0–68.7)**	**279**	**67.4 (62.6–71.9)**
No	20	14.2	33	12.1	53	12.8
I don't know	14	9.9	68	24.9	82	19.8
Ischemic colitis						
Yes	6	4.3	2	0.7	8	1.9
No[a]	**82**	**58.2**	**141**	**51.6**	**223**	**53.9**
I don't know	53	37.6	130	47.6	183	44.2
Psychotic disorders (including confusional state and hallucinations)						
Yes[a]	**111**	**78.7 (71.0–85.2)**	**188**	**68.9 (63.0–74.3)**	**299**	**72.2 (67.6–76.5)**
No	11	7.8	16	5.9	27	6.5
I don't know	19	13.5	69	25.3	88	21.3
QTc prolongation						
Yes[a]	**106**	**75.2 (67.2–82.1)**	**166**	**60.8 (54.7–66.6)**	**272**	**65.7 (60.9–70.3)**
No	12	8.5	31	11.4	43	10.4
I don't know	23	16.3	76	27.8	99	23.9
Rhabdomyolysis						
Yes	6	4.3	13	4.8	19	4.6
No[a]	**69**	**48.9**	**110**	**40.3**	**179**	**43.2**
I don't know	66	46.8	150	54.9	216	52.2

Table 3 continued

Question	RP $N = 141$		RNP $N = 273$		All participants $N = 414$	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Correctly identified all potential risks of TROBALT[b]						
Yes	**60**	**42.6 (34.3–51.2)**	**90**	**33.0 (27.4–38.9)**	**150**	**36.2 (31.6–41.1)**
Question 12: According to the current product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:						
Liver function tests						
Yes	97	68.8	163	59.7	260	62.8
No[a]	**32**	**22.7**	**52**	**19.0**	**84**	**20.3**
I don't know	12	8.5	58	21.2	70	16.9
A comprehensive ophthalmologic examination						
Yes[a]	**123**	**87.2 (80.6–92.3)**	**215**	**78.8 (73.4–83.5)**	**338**	**81.6 (77.6–85.3)**
No	9	6.4	17	6.2	26	6.3
I don't know	9	6.4	41	15.0	50	12.1
Blood pressure assessment						
Yes	35	24.8	49	17.9	84	20.3
No[a]	**78**	**55.3**	**122**	**44.7**	**200**	**48.3**
I don't know	28	19.9	102	37.4	130	31.4
Measurement of plasma creatinine values						
Yes	77	54.6	128	46.9	205	49.5
No[a]	**42**	**29.8**	**52**	**19.0**	**94**	**22.7**
I don't know	22	15.6	93	34.1	115	27.8
Question 13: According to the current product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?						
Immediately stop TROBALT						
Selected	40	28.4	76	27.8	116	28.0
Not selected[a]	**101**	**71.6**	**197**	**72.2**	**298**	**72.0**
Discontinue TROBALT if other suitable treatment options are available						
Selected[a]	**72**	**51.1 (42.5–59.6)**	**129**	**47.3 (41.2–53.4)**	**201**	**48.6 (43.6–53.5)**
Not selected	69	48.9	144	52.7	213	51.4
No action required						
Selected	0	0.0	1	0.4	1	0.2
Not selected[a]	**141**	**100.0**	**272**	**99.6**	**413**	**99.8**
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued						
Selected[a]	**73**	**51.8 (43.2–60.3)**	**147**	**53.8 (47.7–59.9)**	**220**	**53.1 (48.2–58.0)**
Not selected	68	48.2	126	46.2	194	46.9
If TROBALT is continued, the patient should be monitored more closely						
Selected[a]	**54**	**38.3 (30.2–46.9)**	**114**	**41.8 (35.8–47.9)**	**168**	**40.6 (35.8–45.5)**
Not selected	87	61.7	159	58.2	246	59.4

CI confidence interval, *RNP* retigabine non-prescribers, *RP* retigabine prescribers

[a] Correct response

[b] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discoloration) of ocular tissues, including the retina,' 'Pigment changes (discoloration) of the nails, lips, and/or skin,' 'Urinary retention,' 'Psychotic disorders (including confusional state and hallucinations),' and 'QTc prolongation' were selected

Table 4 Responses to questions related to understanding of the retigabine indication: subgroup analysis by primary specialty[a]

Question	Epilepsy or epileptology $N = 35$		Neurology with an interest in epilepsy treatment $N = 158$		General neurology $N = 218$	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Question 10: According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:						
Monotherapy of partial onset seizures	1	2.9	1	0.6	0	0.0
Adjunctive treatment of partial onset seizures	4	11.4	38	24.1	48	22.0
Adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated[b]	**29**	**82.9 (66.4–93.4)**	**118**	**74.7 (67.2–81.3)**	**157**	**72.0 (65.6–77.9)**
Status epilepticus	0	0.0	0	0.0	0	0.0
I don't know	1	2.9	1	0.6	13	6.0

CI confidence interval

[a] Results from participants who declared specialties of Neuropsychiatry and Neurosurgery were omitted due to the low numbers of responses

[b] Correct response

Table 5 Responses to questions related to understanding of the retigabine indication: subgroup analysis by number of patients with epilepsy treated per month

Question	1 to 10 Patients $n = 100$		11 to 50 Patients $n = 218$		51 to 100 Patients $n = 73$		101 or more Patients $n = 23$	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Question 10: According to the product labelling for TROBALT, TROBALT should now only be used as:								
Monotherapy of partial onset seizures	0	0.0	2	0.9	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	28	28.0	47	21.6	13	17.8	2	8.7
Adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated[a]	**66**	**66.0 (55.8–75.2)**	**163**	**74.8 (68.5–80.4)**	**57**	**78.1 (66.9–86.9)**	**21**	**91.3 (72.0–98.9)**
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	6	6.0	6	2.8	3	4.1	0	0.0

CI confidence interval

[a] Correct response

Epileptology ($n = 35$), Neuropsychiatry ($n = 2$), and Neurosurgery ($n = 1$) showed higher correct response rates than the overall analysis results, although the numbers in the latter two specialties (data not shown) were too small to permit meaningful conclusions. Responses from specialists in Neurology with an Interest in the Treatment of Epilepsy ($n = 158$), and General Neurology ($n = 218$) paralleled the overall analysis results. Results of subgroup analysis by the number of patients with epilepsy treated per month (1–10; 11–50; 51–100; $\geq$ 101) (Table 5) showed a higher percentage of correct responses for physicians who were treating higher numbers of patients with epilepsy per month.

Overall, the post hoc subgroup analysis by country paralleled the main analysis results. Physicians who completed the survey were from Spain ($N = 186$, 44.9 %), Slovakia ($N = 66$, 15.9 %), the UK ($N = 63$, 15.2 %), Belgium ($N = 51$, 12.3 %), Switzerland ($N = 29$, 7.0 %), Norway ($N = 17$, 4.1 %), and Hong Kong ($N = 2$, 0.5 %) (Table 2).

4 Discussion

As part of its European post-marketing commitment and RMP, GSK distributed an educational letter to neurologists in the first seven European countries to launch retigabine (Denmark, Germany, Norway, Slovakia, Spain, Switzerland, and the UK), focusing on the risks described in the

approved EU Physician's Guide for retigabine. Results of a follow-up online survey (November 2012–October 2013) to assess the impact of this educational outreach indicated that physicians generally had adequate knowledge of the indication for retigabine, but had poorer recall of specific dose-related information and risk management [12].

The results of the present online survey demonstrate a satisfactory level of awareness of the most important safety issues associated with retigabine, including the risk of retinal pigmentation and potential vision loss. Understanding was stronger among RP than RNP, stronger for physicians who were more specialized in epilepsy management than for general neurologists, and stronger for clinicians who provide care for higher rather than lower numbers of epilepsy patients per month.

Approximately three-quarters of all physicians who responded to the present survey recognized that the current licensed indication for retigabine limits this medication to adjunctive use in patients with partial onset seizures where other appropriate combinations have proved inadequate or have been poorly tolerated. More than 80 % of participants recognized the risk of ocular (including retinal) pigmentation with retigabine and understood that comprehensive ophthalmologic safety assessments were required. In the event of detecting either retinal pigmentation or visual changes, virtually all participants understood that action was required. However, there was a high level of variability in the choice of action identified, possibly driven by a range of different hypothetical patient considerations and the way the question was presented.

The results of this survey indicate that clinicians have a satisfactory current level of awareness of changes in the retigabine product information, and demonstrate that efforts to communicate recognized risks related to the use of retigabine have been effective. In establishing a target sample for the study, it was considered unlikely that retigabine was prescribed by physicians not included on the mailing list for the DHCP letter in June 2013, as the approved labelling restricts retigabine to a patient population treated only by epilepsy specialists. The results should be generalizable, therefore, to the population of RP and clinicians who might use the product.

4.1 Limitations

Although the survey questions were generally straightforward and readily comprehensible, the responses regarding action to take in case of retinal pigmentation or vision changes may have been distorted by the relatively complex construction of question 13, which differed from that of the other questions (see Table 3).

This was a voluntary survey and the sample, while selected, may not be representative of all physicians who prescribe retigabine. The higher number of responses by physicians from Spain could possibly be explained by the exclusive use of e-mail invitations, whereas the invitations by postal mail in other countries may have been subject to administrative or institutional filters. In addition, the mailing list in Spain was larger, providing a larger sample size than in other countries.

The greater difficulty of recruiting RP than RNP for this online survey reflects the relatively modest current use of retigabine internationally. The inclusion of a subpopulation of RP may have biased the overall results through enrichment, as RP might be assumed to have a better understanding of retigabine-associated risks. Finally, physicians taking the survey were not restricted from access to the SmPC or other educational materials, which could have influenced their response. It is possible that a participant could have researched the answers while taking the test; however, in an unmonitored, self-administered survey there is no way to control such behavior, which must be accepted as a limitation of any such study. In the clinical setting, however, physicians are free to consult the SmPC.

5 Conclusion

This seven-country survey of physicians who regularly treat patients with epilepsy followed a DHCP letter as part of the manufacturer's RMP. The results indicated a satisfactory understanding of the most important safety issues associated with retigabine, an adjunctive therapy for drug-resistant partial onset seizures, which is indicated only where other appropriate drug combinations have proved inadequate or have not been tolerated. Most participants recognized the appropriate population for retigabine treatment and were aware of the requirement to monitor for treatment-emergent adverse events including retinal pigmentation and vision changes. The level of understanding appeared higher among physicians who specialized in epilepsy, physicians treating higher rather than lower numbers of epilepsy patients per month, and among retigabine prescribers than non-prescribers, although understanding was also satisfactory in physicians who did not manage patients with this antiepileptic therapy.

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Compliance with Ethical Standards

Ethical approval This study did not include intervention; therefore, institutional review board approval was not deemed necessary. Ethical approval was obtained as required by individual countries, as was regulatory approval or notification where applicable.

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Conflicts of interest J Daniluk, J.A. Cooper, and M. Stender are employees of GSK, the pharmaceutical company that sponsored this research and markets the drug retigabine, and own shares/stock options in GSK. A. Kowalczyk is an employee of United BioSource Corporation (UBC: an Express Scripts Company), which received funding from GSK for the design and conduct of this study. Part of this included the preparation of the final study report. Neither UBC nor AK was paid by GSK for reviewing the manuscript.

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